Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Qureshi AI, Palesch YY, Barsan WG, et al. Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med 2016;375:1033-43. DOI: 10.1056/NEJMoa1603460

Supplementary Appendix
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Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH)-2

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A directory listing US network hubs, hub PIs, site Principal Investigators and study coordinators affiliated with the Neurological Emergency Treatment Trials (NETT) Network is available online: http://nett.umich.edu/directory

Supplementary description 1 (D1). Summary of interim analyses with overwhelming efficacy and futility assumptions

Herein the summary of the interim analyses from the trial is presented. Note that the DSMB remained blinded to treatment throughout. Thus, we produced conditional power under two scenarios of references. It was not until the third interim analysis when both were below the pre-specified threshold that they recommended stopping the study for futility.
Below is the observed values p-values and conditional power at each of the three interim analyses:

INTERIM ANALYSIS SAMPLE	EFFICACY ASSESSMENT: P-VALUE	FUTILITY ASSESSMENT: CONDITIONAL POWER UNDER CURRENT TREND	
		USING TRT=0 AS REFERENCE	USING TRT=1 AS REFERENCE
N=425	0.5280	42.68%	75.42%
N=640	0.9516	29.47%	33.75%
N=850	0.9053	9.11%	4.73%

The planned interim efficacy analysis per the Statistical Analysis Plan was as follows:

For the interim analyses associated with the primary efficacy analysis, O'Brien and Fleming (1979) stopping boundaries are adopted. Assuming that the two interim analyses occur after approximately 425 (1/3 of 1,280 subjects) and 850 (2/3) subjects have completed the 90-day assessments, the nominal alpha levels to reject the null hypotheses for overwhelming efficacy are as follows:

Table 1. Nominal Alpha Levels for Interim Analysis for Overwhelming Efficacy for Overall Sample with N=1,280

Analysis Order	*Number of Subjects*	*Nominal alpha level*
1	*425*	*0.0002*
2	*850*	*0.0120*
Final	*1,280*	*0.0463*

Depending upon the DSMB request, additional interim analyses may be conducted. The spending function approach gives flexibility in the timing and frequency of interim analyses. The most current version of the EAST® software (Cytel Corporation) is used as the interim monitoring tool.

At any interim analysis, if we cross the stopping boundary, the DSMB may recommend stopping the study for overwhelming efficacy of one treatment over the other, although the better treatment may not necessarily be the intensive treatment. If and only if the stopping boundary is crossed, prior to making the final decision for recommendation to stop the study, it is expected that the DSMB would request thorough analyses of secondary outcomes and subgroup analyses to confirm the findings of the primary outcome results.

With the addition of the interim analysis at N=640 subjects, the nominal alpha levels to reject the null hypotheses for overwhelming efficacy are altered slightly:

Analysis Order	Number of Subjects	Nominal alpha level
1	425	0.0002
2 (unplanned)	640	0.0030
3	850	0.0112
Final	1,280	0.0463

For assessment of futility, we adopt the stochastic curtailment method based on conditional power. The informal criterion for determination of futility is that at each interim look, if the conditional power (defined as the probability of rejecting the null hypothesis at the final analysis given the data accumulated so far and under the assumption that the alternative is true) falls below, for example, 10% at the first interim analysis and 20% at the second interim analysis (to be determined in consultation with the DSMB prior to the study initiation), then the DSMB may evaluate all study information (such as overall recruitment rate and secondary outcome assessment data) to consider stopping the study for futility. Depending upon the DSMB request, additional interim analyses may be conducted. Note that email correspondence on January 1, 2015 with the DSMB stated “The DSMB wants to use 20% as the C.P. cutoff at the 1/2 and 2/3 enrollment futility analyses.”

Supplementary description 2 (D2): Method of multiple imputation used to account for missing data

Imputing values for missing data allows using all randomized subjects' data in the outcome analysis. Hence, it is adherent to the intent to treat principle and preserves the statistical power.
Multiple imputation is a method of imputing missing data that incorporates the uncertainty to the imputed values by generating multiple samples (via a computer simulation) of the study data, each with variable imputed values for the missing data. For the primary outcome analysis of ATACH II Trial, multiple imputation using PROC MI in SAS version 9.4 was used for the imputation of missing data by fully conditional specification methods. Binary variables were imputed using logistic regression and continuous variables using linear regression. A specific seed in the imputation was used for reproducibility; there were 10 burn-in iterations; and the covariates and their specified order for the imputation were age, sex, race (coded as dummy variables for ASIAN, BLACK, OTHER with WHITE as the reference), country (coded as dummy variables for JAPAN, CHINA, TAIWAIN, SOUTH KOREA, GERMANY with US as the reference), Glasgow Coma Scale at randomization (coded as dummy variables for 0-11, 12-14 with 15 as the reference), systolic blood pressure at randomization, presence or absence of intraventricular hemorrhage, time between symptom onset to randomization, treatment assignment, death within 24 hours, baseline hematoma volume, and Glasgow Coma Scale at 24 hours (coded as dummy variables for 0-11, 12-14 with reference as 15). One-hundred imputed datasets were generated by the PROC MI procedure which was then analyzed separately using PROC GENMOD and the results were compiled using PROC MIANALYZE.

Supplementary Table 1 (S1). Baseline and treatment characteristics of subjects according to treatment group.

Characteristics	Intensive treatment n=500	Standard treatment n=500
Prior stroke/transient ischemic attack - number/total number (%)	80/500 (16)	84/500 (16.8)
Other prior nervous system disorders - number/total number (%)	23/500 (4.6)	17/500 (3.4)
History of congestive heart failure - number/total number (%)	16/500 (3.2)	21/500 (4.2)
History of atrial fibrillation - number/total number (%)	20/500 (4)	16/500 (3.2)
Myocardial infarction in the previous 3 months - number/total number (%)	1/500 (0.2)	0/500 (0)
History of coronary artery disease¥ - number/total number (%)	27/500 (5.4)	17/500 (3.4)
History of hypertension - number/total number (%)	411/500 (82.2)	382/500 (76.4)
History of peripheral vascular disease - number/total number (%)	9/500 (1.8)	13/500 (2.6)
History of hyperlipidemia - number/total number (%)	122/500 (24.4)	119/500 (23.8)
History of cardiac dysrhythmias - number/total number (%)	17/500 (3.4)	21/500 (4.2)

History of diabetes mellitus Type 2 - number/total number (%)	92/500 (18.4)	83/500 (16.6)
Previous use of antihypertensive drugs - number/total number (%)	260/496 (52.4)	235/497 (47.3)
Symptom onset to randomization time, minutes (mean± standard deviation)	182.2±57.2	184.7±56.7
Symptom onset to nicardipine infusion time[1], minutes (mean± standard deviation)	149±65	165.3±101.3
Mean minimum systolic blood pressure, during the first 2 hours post randomization[2], mm Hg - mean ± standard deviation	128.9±16	141.1±14.8
Failure to attain systolic blood pressure target within 2 hours - number/total number (%)	61/500 (12.2)	4/500 (0.8)
Failure to attain systolic blood pressure target for 2 consecutive hours during 2-24 hours - number/total number (%)	78/500 (15.6)	7/500 (1.4)

[1]24 subjects missing (3 in intensive treatment arm, 21 in standard treatment arm).

[2]3 subjects missing (in standard treatment arm).

Supplementary Table 2 (S2): Adverse events among subjects according to treatment group**.**

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Abdominal abscess	0	0	1	1
Abdominal discomfort	1	1	0	0
Abdominal pain	0	0	3	2
Abscess limb	1	1	0	0
Abscess oral	1	1	0	0
Activated partial thromboplastin time prolonged	0	0	1	1
Acute coronary syndrome	1	1	0	0
Acute myocardial infarction	0	0	2	2
Acute pulmonary oedema	1	1	0	0
Acute respiratory distress syndrome	0	0	1	1
Acute respiratory failure	1	1	4	4
Administration site reaction	1	1	0	0
Agitation	14	13	7	6
Alcohol withdrawal syndrome	1	1	1	1
Alkalosis	0	0	1	1
Altered state of consciousness	1	1	0	0
Amnesia	1	1	1	1
Anaemia	9	9	5	5

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Angioedema	1	1	0	0
Angiopathy	1	1	0	0
Anxiety	3	3	0	0
Aortic stenosis	1	1	0	0
Aphasia	1	1	0	0
Arteriosclerosis	1	1	0	0
Arteriovenous fistula	1	1	1	1
Arthralgia	1	1	1	1
Arthritis	0	0	2	2
Aspiration	3	3	0	0
Asthenia	0	0	1	1
Atelectasis	3	3	2	2
Atrial fibrillation	9	8	2	2
Atrioventricular block complete	1	1	0	0
Atrioventricular block second degree	1	1	0	0
Axillary vein thrombosis	0	0	1	1
Back pain	3	3	3	3
Bacteraemia	2	2	1	1
Benign prostatic hyperplasia	1	1	0	0
Bladder cancer	1	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Blister	0	0	1	1
Blood albumin decreased	1	1	1	1
Blood bilirubin increased	0	0	1	1
Blood calcium decreased	1	1	0	0
Blood chloride abnormal	1	1	0	0
Blood chloride increased	2	2	0	0
Blood cholesterol increased	0	0	1	1
Blood creatinine abnormal	0	0	1	1
Blood creatinine decreased	1	1	0	0
Blood creatinine increased	6	6	3	3
Blood lactate dehydrogenase increased	1	1	0	0
Blood phosphorus decreased	0	0	1	1
Blood potassium decreased	1	1	1	1
Blood pressure decreased	0	0	1	1
Blood pressure diastolic increased	0	0	1	1
Blood pressure increased	0	0	1	1
Blood sodium increased	1	1	0	0
Blood urea decreased	1	1	0	0
Blood urea increased	2	2	3	3
Blood urine present	0	0	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Body temperature increased	0	0	1	1
Bradycardia	3	3	5	5
Brain herniation	2	2	2	2
Brain oedema	8	8	3	3
Brain stem infarction	0	0	1	1
Breast cancer	1	1	0	0
Breast mass	1	1	0	0
Bronchopneumonia	0	0	1	1
Bundle branch block left	1	1	0	0
C-reactive protein increased	1	1	0	0
CNS ventriculitis	0	0	1	1
Cardiac arrest	4	4	2	2
Cardiac failure	2	2	1	1
Cardiac failure acute	0	0	1	1
Cardiac failure congestive	2	2	1	1
Cardiac murmur	1	1	0	0
Cardio-respiratory arrest	0	0	4	4
Cardiopulmonary failure	1	1	0	0
Catheter site pain	0	0	1	1
Cellulitis	6	6	5	5

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Cerebral haematoma	2	2	7	7
Cerebral haemorrhage	2	2	2	2
Cerebral infarction	1	1	1	1
Cerebrovascular accident	22	21	24	23
Cerebrovascular disorder	0	0	1	1
Chest discomfort	2	2	0	0
Chest pain	3	3	4	4
Chills	1	1	1	1
Cholecystitis	2	1	1	1
Cholecystitis acute	1	1	1	1
Cholecystitis infective	0	0	1	1
Chronic obstructive pulmonary disease	4	3	0	0
Circulatory collapse	2	2	0	0
Clostridial infection	1	1	4	4
Clostridium difficile colitis	1	1	0	0
Cognitive disorder	1	1	0	0
Coma	0	0	1	1
Coma scale abnormal	0	0	1	1
Confusional state	1	1	1	1
Consciousness fluctuating	1	1	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Constipation	25	25	25	25
Contusion	1	1	0	0
Convulsion	5	5	10	10
Cough	0	0	1	1
Cranioplasty	0	0	2	2
Craniotomy	0	0	1	1
Cyst aspiration	0	0	1	1
Dacryocystitis	1	1	0	0
Deafness unilateral	0	0	1	1
Death	1	1	1	1
Decubitus ulcer	4	4	2	2
Deep vein thrombosis	4	4	9	9
Dehydration	2	2	1	1
Delirium	8	8	7	7
Delirium tremens	1	1	0	0
Depressed level of consciousness	3	3	1	1
Depressed mood	1	1	0	0
Depression	4	4	1	1
Dermatitis contact	0	0	2	2
Device related infection	1	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Diarrhoea	6	6	2	2
Diastolic dysfunction	1	1	0	0
Diplopia	0	0	3	2
Dizziness	0	0	1	1
Drug eruption	1	1	1	1
Drug withdrawal syndrome	1	1	0	0
Dry skin	1	1	0	0
Dyslipidaemia	3	3	0	0
Dysmenorrhoea	0	0	1	1
Dyspepsia	0	0	2	1
Dysphagia	7	7	6	6
Dyspnoea	5	5	0	0
Dysuria	3	3	2	2
Eczema	0	0	1	1
Electrocardiogram ST segment depression	0	0	1	1
Electrolyte imbalance	7	7	5	5
Embolic cerebral infarction	1	1	0	0
Embolic stroke	0	0	1	1
Encephalopathy	1	1	1	1
Endotracheal intubation	0	0	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Enteritis infectious	1	1	0	0
Enterocolitis viral	1	1	0	0
Epilepsy	1	1	2	2
Epistaxis	1	1	0	0
Erysipelas	0	0	1	1
Erythema	0	0	1	1
Excoriation	2	2	0	0
Extradural haematoma	2	2	0	0
Extrasystoles	1	1	0	0
Fall	6	6	6	6
Fatigue	1	1	0	0
Femoral neck fracture	1	1	0	0
Femur fracture	0	0	2	2
Flatulence	0	0	1	1
Fluid overload	1	1	0	0
Gastric occult blood positive	1	1	0	0
Gastrointestinal haemorrhage	2	2	0	0
Gastrostomy tube insertion	0	0	1	1
Generalised erythema	0	0	1	1
Glomerular filtration rate increased	1	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Glycosylated haemoglobin increased	0	0	1	1
Gout	1	1	3	3
Haematemesis	2	2	1	1
Haematocrit decreased	1	1	0	0
Haematoma	1	1	0	0
Haematuria	4	4	0	0
Haemoglobin decreased	2	2	1	1
Haemorrhage	1	1	3	3
Haemorrhage intracranial	12	11	6	6
Haemorrhage subcutaneous	0	0	2	2
Haemorrhagic anaemia	1	1	1	1
Haemorrhagic infarction	1	1	0	0
Haemorrhagic stroke	1	1	0	0
Hallucination	2	2	0	0
Headache	18	17	25	22
Hemiplegia	0	0	1	1
Hepatic cirrhosis	0	0	1	1
Hepatic cyst	1	1	0	0
Hepatic enzyme increased	1	1	1	1
Hepatic function abnormal	3	3	5	4

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Hepatic steatosis	1	1	0	0
Hydrocephalus	12	12	8	8
Hydronephrosis	1	1	0	0
Hyperbilirubinaemia	1	1	0	0
Hypercapnia	1	1	0	0
Hyperchloraemia	1	1	1	1
Hyperglycaemia	7	7	3	3
Hyperhomocysteinaemia	5	5	4	4
Hyperkalaemia	3	3	5	5
Hyperlipidaemia	4	4	6	6
Hypermagnesaemia	2	2	0	0
Hypernatraemia	10	10	11	11
Hyperphosphataemia	0	0	2	2
Hypersensitivity	3	3	1	1
Hypertension	6	6	7	6
Hypertensive crisis	1	1	0	0
Hypertensive emergency	1	1	0	0
Hypervolaemia	1	1	0	0
Hypoaesthesia	0	0	2	2
Hypoalbuminaemia	5	5	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Hypocalcaemia	7	7	10	10
Hypoglycaemia	2	2	1	1
Hypokalaemia	39	38	32	28
Hypomagnesaemia	4	4	2	2
Hyponatraemia	7	7	17	16
Hypophosphataemia	9	9	8	8
Hypoproteinaemia	0	0	1	1
Hypotension	7	7	4	4
Hypovolaemia	1	1	0	0
Hypoxia	1	1	3	3
IIIrd nerve paralysis	0	0	1	1
Ileus	0	0	2	2
Ileus paralytic	1	1	1	1
Incontinence	1	1	1	1
Infection	1	1	0	0
Insomnia	1	1	2	2
Intracranial aneurysm	0	0	1	1
Intracranial haematoma	3	3	3	3
Intracranial pressure increased	2	1	2	2
Intraventricular haemorrhage	3	3	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Ischaemia	0	0	1	1
Ischaemic cerebral infarction	1	1	0	0
Ischaemic stroke	2	2	2	2
Laboratory test abnormal	1	1	2	2
Laceration	1	1	1	1
Left ventricular hypertrophy	1	1	0	0
Lethargy	1	1	0	0
Leukocytosis	13	13	2	2
Leukopenia	0	0	1	1
Liver disorder	4	4	1	1
Liver function test abnormal	3	3	3	2
Loss of consciousness	1	1	0	0
Lung infection	14	14	16	14
Macular oedema	0	0	1	1
Meningitis	3	2	0	0
Mental impairment	4	4	1	1
Mental status changes	2	2	6	6
Metabolic acidosis	0	0	2	2
Metastasis	1	1	0	0
Monocyte count increased	1	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Muscle spasms	0	0	3	3
Muscular weakness	0	0	2	2
Musculoskeletal pain	2	2	0	0
Myocardial infarction	1	1	1	1
Myocardial ischaemia	1	1	0	0
Nasal congestion	1	1	0	0
Nausea	8	8	7	7
Necrotising colitis	1	1	0	0
Nephropathy	1	1	0	0
Neurogenic bladder	1	1	0	0
Neurological decompensation	26	26	12	12
Neurological symptom	1	1	0	0
Neutrophil count increased	1	1	0	0
Occult blood positive	1	1	0	0
Oedema peripheral	3	3	0	0
Oliguria	1	1	0	0
Oral candidiasis	0	0	1	1
Ovarian cyst	1	1	0	0
Oxygen saturation decreased	3	3	0	0
PO2 decreased	0	0	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Pain	4	4	1	1
Pain in extremity	0	0	2	2
Pancreatitis	1	1	0	0
Paraesthesia	0	0	1	1
Partial seizures	1	1	5	4
Pharyngitis	0	0	1	1
Phlebitis	17	17	18	18
Platelet count decreased	0	0	1	1
Pleural effusion	2	2	0	0
Pneumocephalus	0	0	2	1
Pneumonia	29	27	17	16
Pneumonia aspiration	32	30	20	20
Pneumonia pneumococcal	1	1	0	0
Pneumonia staphylococcal	1	1	0	0
Pneumothorax traumatic	0	0	1	1
Pollakiuria	1	1	0	0
Polyarthritis	0	0	1	1
Post transfusion purpura	0	0	1	1
Presyncope	1	1	1	1
Procalcitonin increased	1	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Pruritus	0	0	1	1
Psychotic disorder	1	1	0	0
Pulmonary congestion	1	1	0	0
Pulmonary embolism	4	4	3	3
Pulmonary oedema	2	2	2	2
Pulseless electrical activity	1	1	0	0
Pyelonephritis chronic	1	1	0	0
Pyrexia	33	31	42	41
Rash macular	0	0	1	1
Rectal cancer	1	1	0	0
Renal cyst	0	0	1	1
Renal failure	3	3	2	2
Renal failure acute	17	17	7	7
Renal failure chronic	1	1	0	0
Renal function test abnormal	0	0	1	1
Renal impairment	6	6	3	3
Renal injury	0	0	1	1
Respiratory arrest	1	1	0	0
Respiratory distress	3	3	3	3
Respiratory failure	10	10	11	11

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Respiratory rate increased	1	1	0	0
Respiratory tract infection	0	0	1	1
Restlessness	2	2	2	2
Retinal degeneration	1	1	0	0
Retinopathy hypertensive	1	1	0	0
Rheumatoid arthritis	0	0	1	1
Schizophrenia, paranoid type	1	1	0	0
Scleral oedema	0	0	1	1
Seizure like phenomena	0	0	1	1
Sepsis	1	1	4	4
Septic shock	1	1	0	0
Sinus bradycardia	0	0	1	1
Sinus tachycardia	1	1	1	1
Sinusitis	1	1	0	0
Skin disorder	1	1	0	0
Skin fissures	0	0	1	1
Sleep apnoea syndrome	2	2	2	2
Sleep disorder	4	4	2	2
Small intestinal obstruction	0	0	1	1
Somnolence	1	1	3	3

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Speech disorder	0	0	1	1
Sputum culture positive	0	0	1	1
Sputum increased	0	0	1	1
Staphylococcal infection	1	1	0	0
Stereotactic surgery	0	0	1	1
Streptococcus test positive	0	0	1	1
Stress ulcer	3	3	3	3
Stroke in evolution	1	1	1	1
Subarachnoid haemorrhage	0	0	1	1
Subdural haematoma	1	1	0	0
Subdural haematoma evacuation	1	1	0	0
Subdural hygroma	0	0	1	1
Supraventricular tachycardia	3	3	0	0
Syncope	2	2	0	0
Tachycardia	9	8	8	8
Tachypnoea	0	0	1	1
Thrombocytopenia	1	1	4	4
Thrombophlebitis superficial	0	0	2	2
Tongue oedema	0	0	1	1
Tonsillitis	1	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Tracheobronchitis	1	1	0	0
Transient ischaemic attack	0	0	1	1
Tremor	2	2	0	0
Troponin I increased	1	1	3	2
Troponin increased	7	6	3	3
Upper gastrointestinal haemorrhage	2	2	4	4
Upper respiratory tract infection	1	1	0	0
Ureteric obstruction	1	1	1	1
Urethral stenosis	1	1	0	0
Urinary incontinence	0	0	1	1
Urinary retention	1	1	4	4
Urinary tract infection	21	21	24	24
Urinary tract infection fungal	1	1	0	0
Urine output decreased	6	6	0	0
Urosepsis	3	3	0	0
Urticaria	1	1	0	0
Vasogenic cerebral oedema	1	1	0	0
Vena cava thrombosis	1	1	0	0
Venous thrombosis	0	0	2	2
Venous thrombosis limb	2	2	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Ventricular extrasystoles	3	3	1	1
Ventricular hypertrophy	0	0	1	1
Ventricular tachycardia	3	3	0	0
Vertigo	1	1	0	0
Vision blurred	0	0	1	1
Vitamin B12 deficiency	1	1	0	0
Vomiting	13	13	11	11
Wheezing	1	1	1	1
White blood cell count increased	4	4	3	3

Supplementary Table 3 (S3): Serious adverse events among subjects according to treatment group**.**

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Abdominal abscess	0	0	1	1
Abdominal pain	0	0	2	1
Abscess oral	1	1	0	0
Acute coronary syndrome	1	1	0	0
Acute myocardial infarction	0	0	1	1
Acute pulmonary oedema	1	1	0	0
Acute respiratory failure	0	0	4	4
Alcohol withdrawal syndrome	1	1	0	0
Angioedema	1	1	0	0
Angiopathy	1	1	0	0
Aphasia	1	1	0	0
Arteriovenous fistula	1	1	0	0
Aspiration	1	1	0	0
Asthenia	0	0	1	1
Atrial fibrillation	2	2	0	0
Back pain	0	0	1	1
Bladder cancer	1	1	0	0
Blood creatinine increased	0	0	1	1
Bradycardia	2	2	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Brain herniation	2	2	2	2
Brain oedema	3	3	2	2
Breast cancer	1	1	0	0
CNS ventriculitis	0	0	1	1
Cardiac arrest	4	4	2	2
Cardiac failure	0	0	1	1
Cardiac failure acute	0	0	1	1
Cardiac failure congestive	1	1	1	1
Cardio-respiratory arrest	0	0	4	4
Cerebral haematoma	1	1	6	6
Cerebral haemorrhage	0	0	1	1
Cerebrovascular accident	17	17	19	19
Cerebrovascular disorder	0	0	1	1
Chest pain	0	0	2	2
Cholecystitis	2	1	0	0
Cholecystitis acute	1	1	1	1
Cholecystitis infective	0	0	1	1
Chronic obstructive pulmonary disease	4	3	0	0
Circulatory collapse	2	2	0	0
Clostridial infection	1	1	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Convulsion	1	1	3	3
Cranioplasty	0	0	2	2
Cyst aspiration	0	0	1	1
Death	1	1	1	1
Deep vein thrombosis	3	3	4	4
Dehydration	2	2	1	1
Depressed level of consciousness	2	2	0	0
Depression	1	1	1	1
Device related infection	1	1	0	0
Drug eruption	1	1	0	0
Drug withdrawal syndrome	1	1	0	0
Dyspnoea	1	1	0	0
Embolic cerebral infarction	1	1	0	0
Embolic stroke	0	0	1	1
Enteritis infectious	1	1	0	0
Epilepsy	0	0	1	1
Extradural haematoma	2	2	0	0
Fall	1	1	0	0
Femoral neck fracture	1	1	0	0
Femur fracture	0	0	2	2

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Gastrointestinal haemorrhage	2	2	0	0
Haematuria	1	1	0	0
Haemorrhage	1	1	2	2
Haemorrhage intracranial	3	3	3	3
Haemorrhagic anaemia	0	0	1	1
Haemorrhagic infarction	1	1	0	0
Haemorrhagic stroke	1	1	0	0
Hemiplegia	0	0	1	1
Hepatic function abnormal	0	0	1	1
Hydrocephalus	7	7	4	4
Hyperkalaemia	1	1	0	0
Hypertension	3	3	1	1
Hypertensive crisis	1	1	0	0
Hypertensive emergency	1	1	0	0
Hypoaesthesia	0	0	1	1
Hyponatraemia	1	1	1	1
Hypotension	1	1	1	1
Hypoxia	0	0	1	1
Ileus paralytic	0	0	1	1
Intracranial pressure increased	2	1	0	0

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Ischaemia	0	0	1	1
Ischaemic cerebral infarction	1	1	0	0
Ischaemic stroke	2	2	2	2
Leukocytosis	1	1	0	0
Liver function test abnormal	1	1	0	0
Lung infection	0	0	2	2
Meningitis	1	1	0	0
Mental impairment	2	2	1	1
Mental status changes	0	0	2	2
Metastasis	1	1	0	0
Myocardial infarction	0	0	1	1
Myocardial ischaemia	1	1	0	0
Necrotising colitis	1	1	0	0
Neurological decompensation	18	18	9	9
Oxygen saturation decreased	1	1	0	0
Pancreatitis	1	1	0	0
Paraesthesia	0	0	1	1
Partial seizures	1	1	1	1
Pleural effusion	1	1	0	0
Pneumonia	9	9	5	5

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Pneumonia aspiration	9	9	5	5
Pneumonia staphylococcal	1	1	0	0
Pneumothorax traumatic	0	0	1	1
Pulmonary embolism	4	4	3	3
Pulmonary oedema	0	0	1	1
Pulseless electrical activity	1	1	0	0
Pyrexia	1	1	2	2
Rectal cancer	1	1	0	0
Renal failure	1	1	1	1
Renal failure acute	4	4	2	2
Renal failure chronic	1	1	0	0
Respiratory arrest	1	1	0	0
Respiratory distress	2	2	1	1
Respiratory failure	10	10	8	8
Respiratory rate increased	1	1	0	0
Schizophrenia, paranoid type	1	1	0	0
Sepsis	1	1	4	4
Septic shock	1	1	0	0
Small intestinal obstruction	0	0	1	1
Somnolence	1	1	1	1

	Intensive Treatment		Standard Treatment	
MedDRA Preferred Term	**Number of Events**	**Number of Subjects**	**Number of Events**	**Number of Subjects**
Stroke in evolution	1	1	1	1
Subdural haematoma	1	1	0	0
Subdural haematoma evacuation	1	1	0	0
Subdural hygroma	0	0	1	1
Syncope	1	1	0	0
Tachycardia	0	0	1	1
Transient ischaemic attack	0	0	1	1
Upper gastrointestinal haemorrhage	1	1	0	0
Ureteric obstruction	1	1	1	1
Urethral stenosis	1	1	0	0
Urinary tract infection	1	1	0	0
Urosepsis	3	3	0	0

Supplementary Table 4 (S4): Results of analysis performed after grouping the related events (events that represent the same condition of interest by body system) classified using Medical Dictionary for Regulatory Activities (MedDRA) terminology terms.

	Intensive treatment N (%)	Standard treatment N (%)	Unadjusted RR (95% CI)	Adjusted RR (95% CI)‡
Serious renal AE within 7 days	4 (0.8%)	1 (0.2%)	4.00 (0.45, 35.79) p= 0.2150	4.50 (0.50, 40.65) p= 0.1804
Serious renal AE within 30 days	5 (1.0%)	4 (0.8%)	1.25 (0.34, 4.65) p= 0.7394	1.45 (0.38, 5.54) p= 0.5905
Serious renal AE greater than 30 days	1 (0.2%)	0 (0.0%)	NE*	NE*
Any renal AE within 7 days	45 (9.0%)	20 (4.0%)	2.25 (1.33, 3.81) p= 0.0025	2.32 (1.37, 3.94) p= 0.0018
Serious cardiac AE within 7 days	11 (2.2%)	7 (1.4%)	1.57 (0.61, 4.05) p= 0.3499	1.66 (0.64, 4.28) p= 0.2988
Serious cardiac AE within 30 days	13 (2.60%)	10 (2.00%)	1.30 (0.57, 2.96) p= 0.5328	1.37 (0.60, 3.14) p= 0.4527
Serious cardiac AE greater than 30 days	7 (1.40%)	5 (1.00%)	1.40 (0.44, 4.41) p= 0.5655	1.50 (0.48, 4.75) p= 0.4880
Any cardiac AE within 7 days	57 (11.4%)	42 (8.4%)	1.36 (0.91, 2.02) p= 0.1332	1.40 (0.94, 2.08) p= 0.1004
Serious brain hemorrhage AE within 7 days	19 (3.8%)	26 (5.2%)	0.73 (0.40, 1.32) p= 0.2987	0.72 (0.40, 1.30) p= 0.2698
Serious brain hemorrhage AE within 30 days	22 (4.4%)	29(5.8%)	0.76 (0.44, 1.32) p= 0.3285	0.75 (0.43, 1.31) p= 0.3114
Serious brain hemorrhage AE greater than 30 days	2 (0.4%)	1 (0.2%)	2.00 (0.18, 22.06) p= 0.5714	2.15 (0.19, 24.02) p= 0.5340
Any brain hemorrhage AE within 7 days	39 (7.8%)	40 (8.0%)	0.98 (0.63, 1.52) p= 0.9104	0.98 (0.63, 1.52) p= 0.9192
Serious brain infarction AE within 7 days	4 (0.8%)	0 (0.0%)	NE*	NE*
Serious brain infarction AE within 30 days	4 (0.8%)	1 (0.2%)	4.0 (0.45, 35.79) p= 0.2150	3.63 (0.41, 32.55) p= 0.2488
Serious brain infarction AE greater than 30 days	0 (0.0%)	3 (0.6%)	NE*	NE*

Any brain infarction AE within 7 days	5 (1.0%)	1 (0.2%)	5.00 (0.58, 42.80) p= 0.1418	5.16 (0.60, 44.39) p= 0.1348

‡Analysis adjusted for age, baseline Glasgow Coma Scale, and presence/absence of intraventricular hemorrhage at baseline. Abbreviations used: RR, relative risk; CI, confidence interval.

* Some of the adjusted analyses resulted in convergence issues due to the small numbers of events and thus the estimates were not estimable (NE).

Adverse events' reporting was mandatory up to day 7 or discharge, which ever came first.

The adverse events that were deemed indicative of a renal event were:

MEDDRA PREFERRED TERM	MEDDRA CODE
Glomerular filtration rate increased	10018359
Blood urea decreased	10005850
Urinary retention	10046555
Renal function test abnormal	10061480
Renal failure acute	10038436
Renal failure chronic	10038444
Blood urea increased	10005851
Urine output decreased	10059895
Blood creatinine increased	10005483
Renal failure	10038435
Hypervolaemia	10020919
Renal impairment	10062237
Fluid overload	**10016803**
Renal injury	10061481
Blood creatinine decreased	10005482
Blood creatinine abnormal	10005481
Hypovolaemia	10021137
Hydronephrosis	10020524

The adverse events that were deemed indicative of a cardiac event were:

MEDDRA PREFERRED TERM	MEDDRA CODE
Tachycardia	10043071
Acute myocardial infarction	10000891
Hypotension	10021097
Chest pain	10008479
Myocardial ischaemia	10028600
Ventricular tachycardia	10047302
Bradycardia	10006093
Troponin increased	10058267
Hypertension	10020772
Ventricular hypertrophy	10047295
Atrial fibrillation	10003658
Cardiac murmur	10007586
Electrocardiogram ST segment depression	10014391
Angiopathy	10059245
Myocardial infarction	10028596
Cardiac failure	10007554
Chest discomfort	10008469
Sinus tachycardia	10040752
Ventricular extrasystoles	10047289
Supraventricular tachycardia	10042604
Cardiac failure congestive	10007559
Blood pressure increased	10005750
Left ventricular hypertrophy	10049773
Sinus bradycardia	10040741
Circulatory collapse	10009192
Extrasystoles	10015856
Hypertensive emergency	10058179

Cardiac arrest	10007515
Cardio-respiratory arrest	10007617
Atrioventricular block second degree	10003677
Pulseless electrical activity	10058151
Diastolic dysfunction	10052337
Cardiac failure acute	10007556
Bundle branch block left	10006580
Troponin I increased	10058268
Blood pressure diastolic increased	10005739
Atrioventricular block complete	10003673
Aortic stenosis	10002906
Blood pressure decreased	10005734
Acute coronary syndrome	10051592
Hypertensive crisis	10020802
Cardiopulmonary failure	10051093

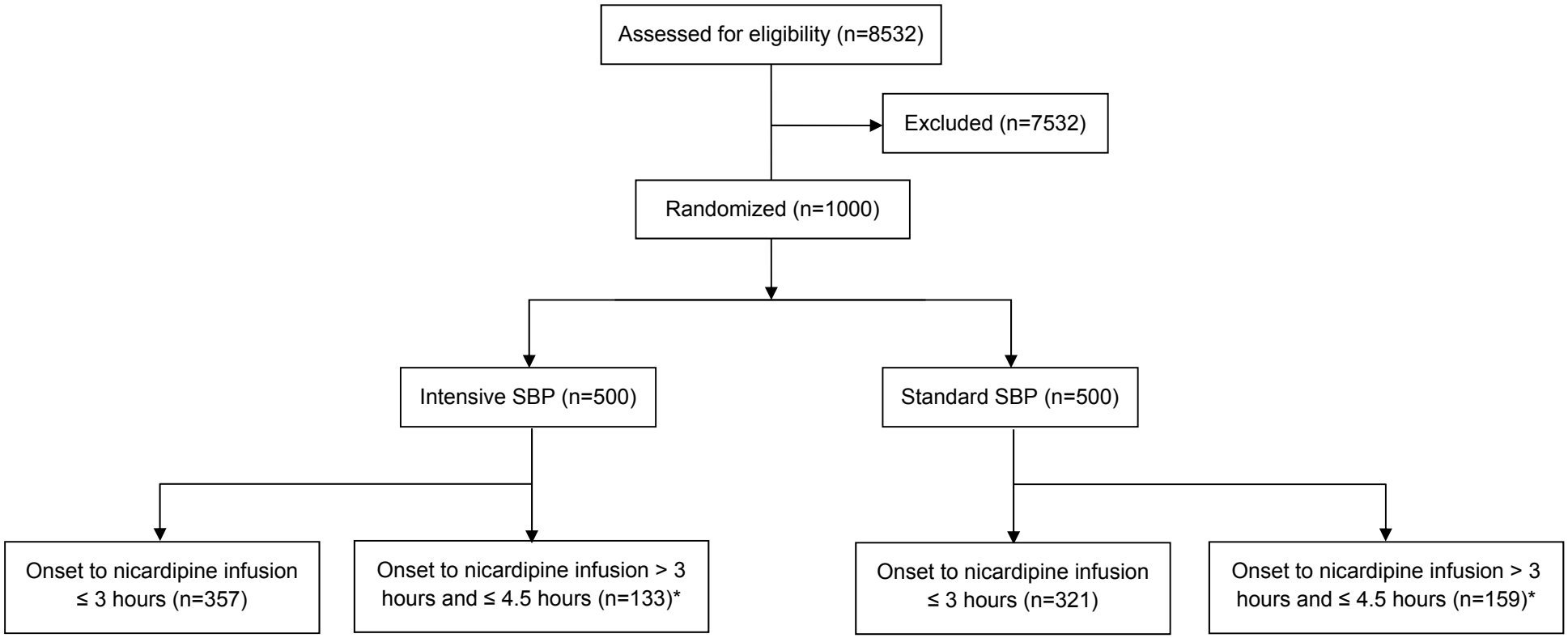
The adverse events that were deemed indicative of any brain infarction were:

MEDDRA PREFERRED TERM	MEDDRA CODE
Brain stem infarction	10006147
Cerebral infarction	10008118
Ischaemic cerebral infarction	10060840
Embolic stroke	10014498
Embolic cerebral infarction	10060839
Ischaemia	10061255
Ischaemic stroke	10061256

The adverse events that were deemed indicative of any brain hemorrhage were:

MEDDRA PREFERRED TERM	MEDDRA CODE
Cerebral haemorrhage	10008111
Cerebrovascular accident	10008190
Extradural haematoma	10015769
Haemorrhage intracranial	10018985
Haemorrhagic infarction	10019013
Haemorrhagic stroke	10019016
Intraventricular haemorrhage	10022840
Subarachnoid haemorrhage	10042316
Subdural haematoma	10042361
Cerebral haematoma	10053942
Haemorrhage	10055798
Intracranial haematoma	10059491

Supplementary Figure 1, The CONSORT Flow diagram to demonstrate progress through the phases of the trial



*10 subjects in intensive group and 20 in standard group have time from onset to nicardipine infusion longer than 4.5 hours